

REVIEW



Contemporary management of major haemorrhage in critical care

Cheryl L. Maier¹, Karim Brohi², Nicola Curry^{3,4}, Nicole P. Juffermans⁵, Lidia Mora Miquel⁶, Matthew D. Neal⁷, Beth H. Shaz⁸, Alexander P. J. Vlaar⁹ and Julie Helms^{10*} 

© 2024 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Haemorrhagic shock is frequent in critical care settings and responsible for a high mortality rate due to multiple organ dysfunction and coagulopathy. The management of critically ill patients with bleeding and shock is complex, and treatment of these patients must be rapid and definitive. The administration of large volumes of blood components leads to major physiological alterations which must be mitigated during and after bleeding. Early recognition of bleeding and coagulopathy, understanding the underlying pathophysiology related to specific disease states, and the development of individualised management protocols are important for optimal outcomes. This review describes the contemporary understanding of the pathophysiology of various types of coagulopathic bleeding; the diagnosis and management of critically ill bleeding patients, including major haemorrhage protocols and post-transfusion management; and finally highlights recent areas of opportunity to better understand optimal management strategies for managing bleeding in the intensive care unit (ICU).

Keywords: Massive transfusion, Haemorrhage, Critical illness, Bleeding, Coagulopathy

Introduction

Major bleeding is commonly encountered in critical care settings, with a reported incidence ranging from 5 to over 50%, and continues to have a high associated morbidity and mortality [1–3]. Assessing accurate rates of major bleeding in different patient populations has been challenging, at least in part due to variability in definitions or criteria used to define it. The International Society on Thrombosis and Haemostasis (ISTH) defines major bleeding as symptomatic bleeding in a critical area or organ, and/or bleeding that causes a fall in haemoglobin of ≥ 2 g/dL or leads to the transfusion of ≥ 2 units of whole blood or red blood cells [4].

Bleeding and haemorrhagic shock lead to the development of altered haemostasis and coagulopathy, which may be exacerbated or complicated by comorbidities or underlying disease states present in critically ill patients. The management of these patients is complex, and strategies to mitigate bleeding must be rapid and definitive. In addition, the administration of large volumes of blood components, which may or may not be balanced in terms of the amount red blood cells, platelets and plasma products transfused, can lead to major physiological alterations that must be mitigated during and after bleeding. Early recognition of bleeding and coagulopathy, understanding of the pathophysiology in specific disease states and effective individualised management are important to secure the optimal outcomes.

The overall objective of this review is to describe the contemporary understanding of the pathophysiology, diagnosis and management of patients with major bleeding in the intensive care unit (ICU) setting. We first review the pathophysiology of various types of

*Correspondence: Julie.helms@chru-strasbourg.fr

¹⁰ Service de Médecine Intensive-Réanimation, Department of Intensive Care, Nouvel Hôpital Civil, Université de Strasbourg (UNISTRA), 1, Place de L'Hôpital, 67091 Strasbourg Cedex, France

Full author information is available at the end of the article



SHOUT
SHARE **IT**

coagulopathic bleeding typically encountered in critical illness, including in patients with trauma, post-partum haemorrhage, chronic liver disease, disseminated intravascular coagulation and uraemia. We next discuss the diagnosis and evaluation of critically ill patients with coagulopathic bleeding and then describe major haemorrhage protocols relevant for those with substantial haemorrhage. Given the unique considerations necessary for patients after experiencing massive haemorrhage, we summarise post-transfusion management, including circulatory support and prevention of thromboembolic events. Finally, we highlight additional considerations and areas of opportunity to better define optimal bleeding management strategies in the ICU.

Pathophysiology of haemorrhagic coagulopathies

The different pathological processes leading to bleeding result in different patterns of coagulopathy that must be understood to deliver optimal management. Whilst there are areas of overlap, and it may be attractive to simplify management into a single massive haemorrhage protocol (MHP), critical differences must be appreciated to ensure haemostasis is achieved without immediate or downstream complications.

Trauma-related bleeding

Patients with a higher injury severity and those with hypovolemic shock are at the greatest risk of severe bleeding [5]. Multiple coagulation abnormalities, which may result in trauma-induced coagulopathy (TIC), contribute to ineffective haemostasis early after trauma. The central features of TIC are increased fibrinolysis, activation of the protein C pathway, platelet dysfunction and consumption of clotting factors. These are accompanied by endothelial activation with increased microvascular permeability and loss of the endothelial glycocalyx. Hyperfibrinolysis is one of the most common changes reported after severe injury and may accompany even mild or moderate injury [6]. Increased fibrinolysis is likely mediated by increased plasmin activity resulting from high levels of tissue plasminogen activator (tPA) released by activated endothelial cells. Fibrinogen levels fall to critically low levels early during trauma-related haemorrhage, a consequence of increased fibrinogen breakdown (fibrinogenolysis), widespread consumption of fibrinogen, and the dilutional effects of resuscitation fluids [7]. Hypofibrinogenemia may also reflect, or be exacerbated by, a low fibrinogen reserve. High levels of activated protein C (APC) are also thought to be one of the central effectors of the early hypocoagulable state. APC causes inhibition of FVa and FVIIIa, reducing thrombin generation, and also binds to plasminogen activator inhibitor-1, preventing its inhibitory effect on t-PA

Take-home message

Bleeding is a common complication encountered in critical care and necessitates an understanding of the pathophysiology of various coagulopathic conditions to provide appropriate patient care.

and thereby enabling fibrinolysis to continue unchecked. Platelet dysfunction is present with globally reduced aggregation, often described as “platelet exhaustion,” which adds to the hypocoagulable state. Mechanisms of platelet dysfunction are not well understood, though recent evidence points to defective calcium mobilisation, GpVI alterations, or direct attack by damage released histones. Direct injury, shock, catecholamine release and hypoxia all contribute to endothelial activation, whilst alterations in blood rheology are thought to underlie the disruption of the endothelial glycocalyx.

Post-partum haemorrhage

The coagulopathy associated with post-partum haemorrhage (PPH) has yet to be studied in as much detail as TIC. Most cases of PPH are not associated with coagulopathy, although large volume haemorrhage (i.e. over 3 L) has been associated with dilutional or consumptive coagulopathy. “Acute Obstetric Coagulopathy”—similar to the complex multifactorial coagulopathy seen in TIC and characterised by massive fibrinolysis—is much less common [8], occurring in 1.06/1000 pregnancies. Pregnancy is associated with large elevations in circulating fibrinogen levels, and a fibrinogen level below 2 g/L

Table 1 Coagulation defects in compensated chronic liver disease

	Pro-thrombotic	Anti-thrombotic
Primary haemostasis	↑VWF ↓ADAMTS13 Platelet dysfunction	Platelet dysfunction Thrombocytopenia ↑NO ↑Prostacyclin ↓Thrombopoietin
Secondary haemostasis	↑FVIII ↓Proteins C & S ↓AT	↓FII, FV, FVII, FIX, FX, FXI Dysfibrinogenemia ↓Fibrinogen
Fibrinolysis	↓Plasminogen ↑PAI-1	↑tPA ↓α2-AP ↓FXIII ↓TAFI

ADAMTS13 is a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, α2-AP α2-antiplasmin, NO nitric oxide, TAFI thrombin-activatable fibrinolysis inhibitor, tPA tissue-type plasminogen activator, VWF von Willebrand factor

at the onset of PPH is strongly associated with a greater need for large volume transfusion [9] (Table 1). Two clear clinical situations where acute obstetric coagulopathy occurs include amniotic fluid embolism and placental abruption. Acute obstetric coagulopathy shares features with TIC in that it manifests with a profound and rapid reduction in fibrinogen levels and overt hyperfibrinolysis [8]. Dysfibrinogenemia is also detected in these obstetric patients, which is not a confirmed feature of TIC. Therefore, fibrinogen measurement and adequate replacement is critical in caring for these patients.

Chronic liver disease

Approximately one in every eight patients with chronic liver disease (CLD) who are managed in the ICU will develop significant bleeding, as defined by ISTH [10]. Three-quarters of events are gastrointestinal bleeding [11], and in more than 90% of these cases, portal hypertension is the underlying cause. CLD is associated with coagulation factor deficiencies, platelet dysfunction and hyperfibrinolysis [12] (Table 1). However, there are also pro-haemostatic changes in these systems which tend to balance out these hypocoagulable tendencies. Whilst routine laboratory tests commonly show thrombocytopenia as well as prolongation of the prothrombin time (PT), patients with compensated CLD are not at greater risk of bleeding or protected from thrombosis. Patients do, however, have a reduced clotting reserve with little resilience to illness or injury. If decompensation or an insult, such as infection, occurs, patients are at risk of both bleeding and thrombosis [12]. Despite the complexities of coagulation derangements in CLD, the most common reason for an acute bleed is a variceal bleed, and successful management prioritises clinical treatment to reduce portal pressure rather than large volume resuscitation and correction of measured functional coagulation deficits [13].

Disseminated intravascular coagulopathy

Disseminated intravascular coagulopathy (DIC) is an acquired condition that is always secondary to an underlying condition, most often sepsis but also others, like malignancy, trauma or obstetric complications. DIC is characterised by systemic activation of coagulation that leads to widespread formation of intravascular fibrin-rich thrombi, causing occlusion of small- and mid-size vessels and subsequent organ dysfunction [14]. The complex pathophysiology of DIC can result in prothrombotic, bleeding or mixed phenotypes [14, 15]. In addition to depletion of platelets and coagulation factors, levels of physiologic anticoagulants, such as antithrombin and protein C, are decreased due to consumption and extravasation from increased microvascular permeability.

Significantly elevated fibrin degradation products and the systemic inflammatory state cause platelet dysfunction and interfere with fibrin cross-linking, which further contribute to bleeding. Patients with DIC may develop major haemorrhage, depending on the phenotype of the DIC [14]; therefore, the treatment of DIC depends on its phenotype and the underlying disease.

Uraemia

Uraemic bleeding is a well-recognised complication in patients with chronic renal failure [16]. Unfortunately, despite being a relatively common cause of bleeding, little is known about the underlying mechanism. Platelet dysfunction appears to be the dominant abnormality. This is believed to be a consequence of multiple changes that include von Willebrand factor dysfunction (a reduced ability to bind to the platelet glycoprotein GPIb) that reduces platelet tethering to the sites of vessel injury, and complex alterations in key platelet agonist signalling pathways [17]. The latter includes decreased production of thromboxane, increased prostacyclin I₂, increased levels of cyclic AMP/GMP, increased levels of uraemic toxins, and altered platelet granules, all of which are necessary for normal platelet aggregation. Therefore, transfusing platelets into this setting does not correct the platelet dysfunction.

Acquired coagulopathy secondary to anticoagulation

Many critically ill patients receive anticoagulation either as thromboprophylaxis or for therapeutic anticoagulation related to their acute or underlying disease. Bleeding may be the primary reason for ICU admission or may develop during the ICU stay. A multicentre retrospective French study reported that the incidence of patients admitted to the ICU for severe extracranial bleeding related to anticoagulants increased from 3.2/1000 admissions in 2007 to 5.8/1000 in 2018, with an ICU mortality rate of 27% [18]. In this cohort, patients had been using vitamin K antagonists (VKA, 54%), heparins (25%) or direct oral anticoagulants (DOAC, 7%) prior to hospitalisation. Anticoagulant-related extracranial bleeding requiring ICU admission is a serious complication of anticoagulant therapy which may result in organ failure and significant mortality. Unfortunately, current therapeutic management is often suboptimal, which is at least in part related to limitations in laboratory monitoring, lack of experience in clinical management or lack of reversal technologies for certain therapeutic agents. Education and development of anticoagulation reversal agents and protocols, in addition to more accessible laboratory measures of haemostasis on patients on anticoagulation therapy, are needed.

Table 2 Laboratory parameters useful in the evaluation of bleeding conditions typically encountered in the ICU

Bleeding condition	Related pathophysiology	Laboratory testing
Disseminated intravascular coagulation	Deficit of coagulation factors and platelets Loss of physiologic anticoagulants Endothelial dysfunction Thromboinflammation	Platelet count, PT/INR, aPTT, fibrinogen, D-dimer Antithrombin, Protein C
Chronic liver disease	Deficit of fibrinogen Deficit of additional coagulation factors	Fibrinogen level, PT/INR, aPTT VET
Uraemia	Platelet dysfunction	PFA or other platelet function test, if available
Post cardiac surgery	Presence of heparin Hyperfibrinolysis Platelet dysfunction	Anti-Xa or aPTT, ACT VET
Post-partum haemorrhage	Deficit of fibrinogen Hyperfibrinolysis	Fibrinogen level VET
Bleeding under Anticoagulation therapy	Low thrombin generating capacity	PT/INR, anti-Xa or aPTT, dTT or ECT
Non-coagulopathic	Surgical GI Other	Haemoglobin/haematocrit, otherwise normal laboratory parameters

ACT activated clotting time, aPTT activated partial thromboplastin time, ECT ecarin clotting time, GI gastrointestinal, INR International Normalised Ratio, PT prothrombin time, VET viscoelastometric testing

Diagnosis and evaluation

Early recognition of bleeding in critically ill patients is essential to avoid the development of shock and organ failure. Unfortunately, this may not be straightforward given the various underlying conditions present in ICU patients. Assessment of several clinical and laboratory parameters associated with haemorrhagic shock, such as new or worsening tachycardia, tachypnoea, or narrowing pulse pressure, which are physiological responses to low blood volume, may be early clinical signs of significant hypovolemia [1]. A sudden increase in lactate or base deficit may be useful as a trigger for when to initiate treatment [19]. However, all of these parameters may be masked by other haemodynamic disturbances, including systemic inflammatory response syndrome, septic shock, cardiogenic shock and the use of inotropic and vasopressor agents. On occasion, abnormalities noted on laboratory tests, such as a decreased platelet count or prolongation of prothrombin time (PT)/activated partial thromboplastin time (aPTT), may alert providers to the developing coagulopathy. Whilst a decrease in haemoglobin is expected, it is important to note that haemoglobin may not fall acutely due to the severity of bleeding and delay in compensatory mechanisms. Indeed, the presence of haemodynamic decompensation with normal blood count or coagulation parameters may be a definitive sign of uncontrolled occult bleeding requiring surgical or similar intervention. Ultimately, it is important to maintain a high index of suspicion, and to look for and rule out bleeding as a cause of clinical decompensation.

Recognising the severity and underlying aetiology of a patient's coagulopathy are also important to appropriately

manage and individualise care. Conventional laboratory tests including PT, aPTT, fibrinogen levels and the presence of fibrin degradation products (e.g. D-dimer) are the mainstay of diagnosis (Table 2). An increasing D-dimer over 2 days has recently been identified as a practical marker for the prediction of acute fibrinolytic activity preceding the occurrence of a haemorrhagic complication in patients on extracorporeal membrane oxygenation (ECMO) [20]. Functional point-of-care viscoelastic tests (thromboelastometry) may provide a faster and more complete picture of the coagulopathy to direct interventions, assess their effectiveness and guide treatment. The use of viscoelastic tests together with algorithms for coagulation management has shown benefit in managing haemorrhage in cardiac surgery [21] and may be helpful in obstetric [22, 23], liver [24, 25] and other patient populations. Viscoelastic tests may help diagnose hyperfibrinolysis, although with low sensitivity. As an example, Levrat et al. [26] detected hyperfibrinolysis only in 6% of their patients (5 out of 83 true positive patients) using rotational thromboelastometry (ROTEM) and the ELT (euglobulin lysis time) as the gold standard reference. It was found that patients with a short ELT (diagnosis of hyperfibrinolysis) correlate with maximum clot firmness (MCF) and the amplitude of clot at 10 and 15 min, which are indirect graphical parameters. It is important to note that the ELT is not routinely performed in most laboratories given major challenges associated with the assay methodology. Finally, many critically ill patients have coagulation derangements as a function of their disease that will normalise with management of the underlying condition. Thus, in the absence of acute or impending

bleeding, coagulation abnormalities may not require correction.

Major haemorrhage protocols

The acute management of critically ill patients with major bleeding and associated coagulopathy requires the delivery of standardised, evidence-based care that involves multiple hospital teams [27–32]. The complexity can be reduced by having an agreed upon major haemorrhage protocol (MHP) (massive haemorrhage protocol, also known as massive transfusion protocol), although these are not yet universally adopted [33]. MHP implementation has been shown to promote patient survival and minimise complications of massive transfusion, which is typically defined as transfusion of at least 10 red blood cell (RBC) units within 24 h [32, 34–37]. MHPs were initially developed for treating major haemorrhage in trauma patients, and have been adapted for other clinical settings.

Although MHPs have optimised patient care in massive haemorrhage, some components may be based on biased observational studies [38]. One example is the high plasma-to-RBC ratio, which was suggested to have a large reduction in mortality (some from 65 to 19%) [39]. After performing a time-dependent analysis, the mortality effect disappeared [40]. Although no randomised trial was able to confirm the conclusions of the initial observational studies, the high plasma-to-RBC ratio has received widespread implementation, including expansion to massively bleeding non-trauma patients. In a review of high versus low plasma-to-RBC ratio use at a single US hospital, where more than 90% of the massively transfused patients were not trauma patients, high plasma-to-RBC ratio was not associated with an improved outcome [41]. Notably, RBC transfusion alone provides no support for associated coagulopathy and even contributes to dilutional coagulopathy. Therefore, plasma and platelets are important, once large volumes of RBCs have been transfused to prevent or correct coagulopathy.

D-negative females of childbearing potential (FCP—women below 50 years old) who cannot wait for type-specific or cross-matched blood usually receive blood group O RhD negative (RhD–) RBCs, until their blood group is determined, to prevent alloimmunisation and future development of RhD+–related haemolytic disease of the foetus and newborn (HDFN). However, the risk of serious morbidity or mortality resulting from traumatic haemorrhage should be prioritised over potential risk of alloimmunisation (20% for emergency transfusion). The risk of transfusing RhD-positive blood was indeed considered to be low in the prehospital setting [42]. Another study looking at FCP trauma patients who received

RhD-positive RBCs showed the risk of having a pregnancy affected by HDFN might be higher if the FCP was younger when she received her RhD-positive RBC transfusion [43].

A number of products are now being included in MPHs, particularly in the trauma setting. Due to limited availability of group AB plasma and the surge in demand of this product, group A plasma is being used. Data to date support the use of group A plasma, likely due to the fact that patients are receiving group O RBCs. Another recent change is the adoption of group O low titre whole blood for the immediate management of traumatic haemorrhage [44]. These products have low titre anti-A and anti-, although no standard titre is being used. Lastly, cold stored platelets, which have a 14-day shelf life, are being used. Cold stored platelets are already partially activated, and thus are cleared within 24 h [45]. This product may be more effective in the haemorrhagic setting, but clinical trials are still ongoing.

MHPs including pre-specified product ratios allow physicians to have time to control bleeding, minimise the use of crystalloids and understand the coagulopathy, to develop a more personalised treatment as soon as possible. The development of a protocol-based structure for the delivery of blood products, laboratory testing algorithms and other aspects of patient care (such as use of medications, like tranexamic acid, or blood warmers, to prevent hypothermia) remains essential to ensure immediate action in severe and emergent cases. In addition, these protocols rely on teamwork, situational awareness, communication, task definition, allocation and decision making [32, 46, 47]. MHPs should be designed as a multidisciplinary and consensual protocol, with the hospital transfusion committee oftentimes best poised to lead. The content design of the protocol should be adapted to the capabilities of each hospital and following the policies and regulations of each training centre or organisation. The protocol should detail the procedures and criteria for triggering the alert by the treating providers at the bedside and the supply of blood products by the transfusion service. The committee should clearly define quality indicators and review criteria, such as product wastage, patient outcomes, laboratory testing, as well as appropriateness of protocol activations [30, 36, 48, 49]. MHP practise, outcome and utilisation review should occur regularly, with protocol updates to incorporate new evidence and improve local practise.

A central aspect of MHPs is the streamlined delivery of blood and blood component therapy to patients. Once activated, the transfusion service must be able to provide the necessary blood products quickly and consistently. This requires effective communication between the transfusion service and clinical teams, without unnecessary

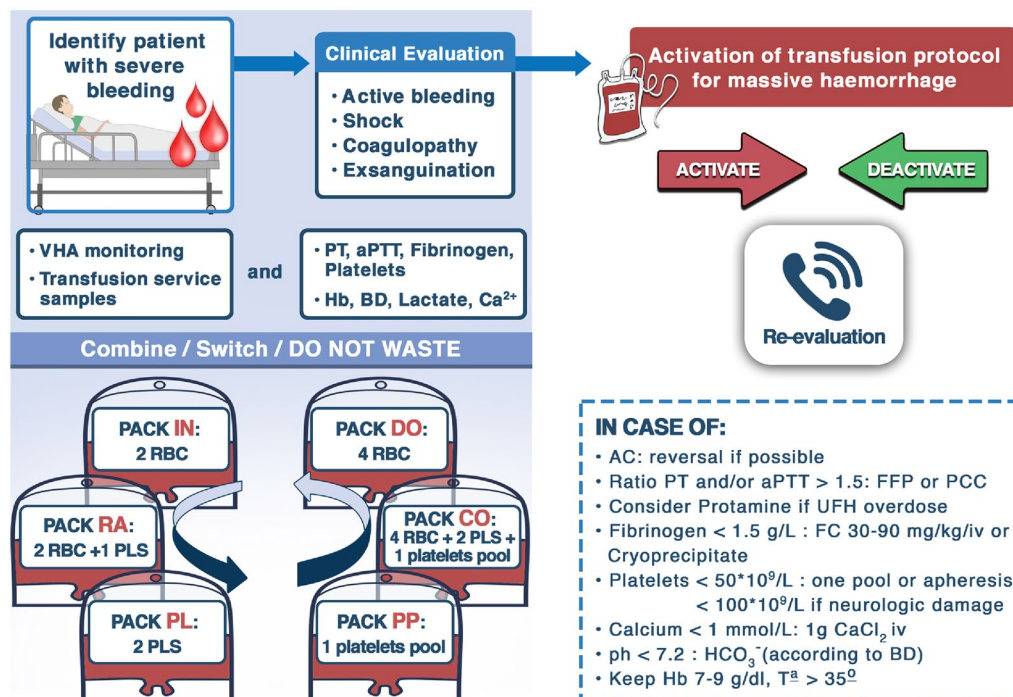


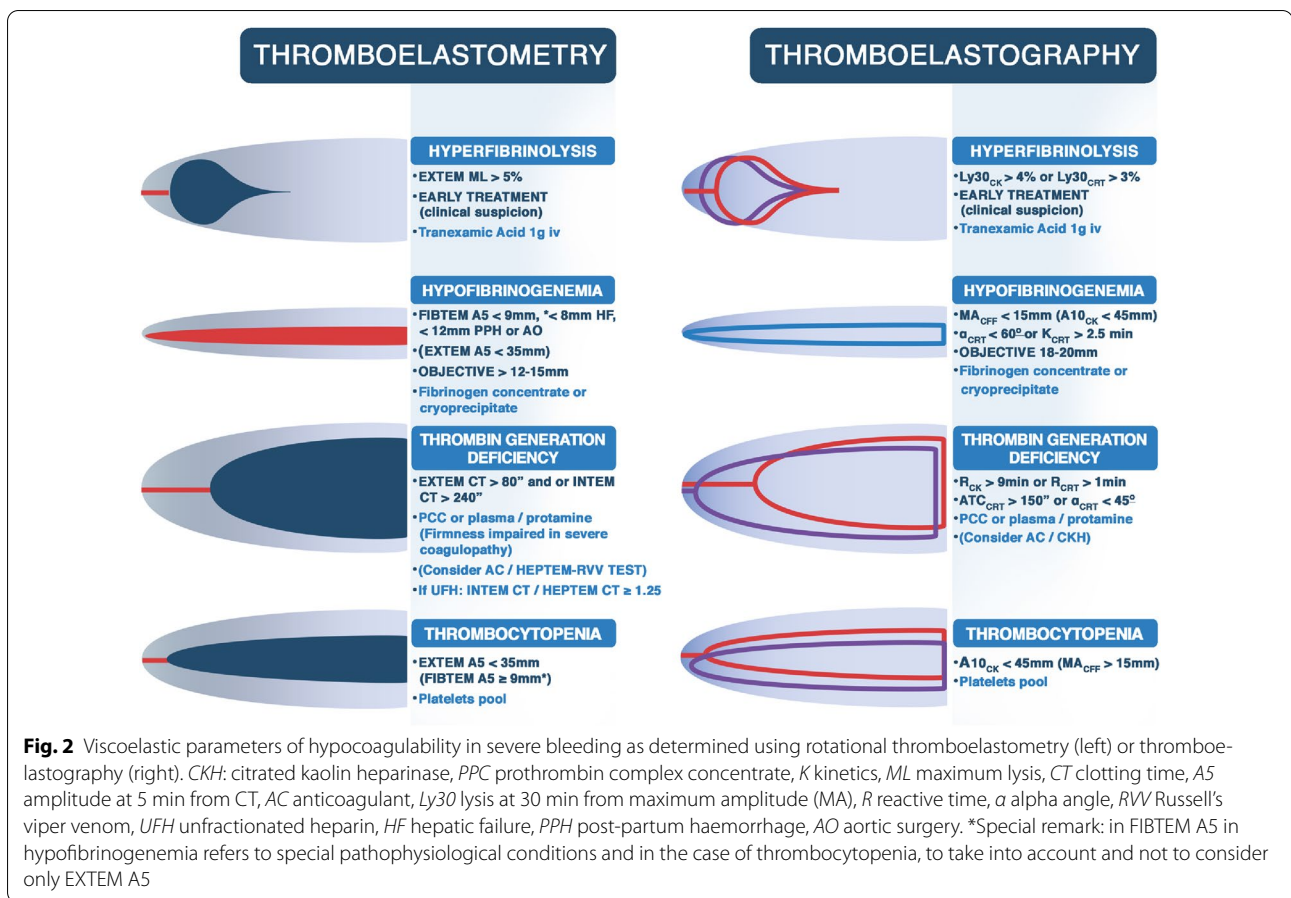
Fig. 1 Schematic overview of a massive haemorrhage protocol. The protocol should be initiated after or alongside measures to stop or control bleeding (e.g. surgery, endoscopy, embolization), which are key elements of major bleeding treatment. Additional elements may be relevant in protocols for certain types of haemorrhage; for example, the inclusion of tranexamic acid in protocols specific for trauma or post-partum haemorrhage. VHA viscoelastic assays, PCC prothrombin complex concentrate, PLS plasma unit, RBC red blood cell unit, PT prothrombin time, aPTT activated partial thromboplastin time, Hb haemoglobin, BD base deficit, IN initial pack, DO double initial pack, CO complete pack, PL plasma pack, PP platelet pack, AC anticoagulant, iv intravenous, FC fibrinogen concentrate, UFH unfractionated heparin

or repeated calls or checks by multiple parties [46, 47]. Most protocols will deliver a baseline balanced transfusion of RBCs and component therapies (plasma, platelets) in empiric packs, which are augmented with addition therapies as required. Emergency group O red blood cells (RBCs) should be provided for patients without the need for a confirmed blood type. Most MHPs have supported the use of damage-control resuscitation principles, including high plasma-to-RBCs and platelet-to-RBCs ratios [50]. Example MHP packs would include 4 units of RBCs and 4 units of plasma, and may include platelet or cryoprecipitate components (Fig. 1). Over the last few years, some healthcare organisations have begun using whole blood. Whole blood contains RBCs, plasma and platelets, allowing easier administration over separate blood components whilst decreasing additional fluid administration [51]. However, whole blood is not universally available and component therapy may still be more appropriate in some hospital settings.

Contemporary guidelines recommend that empiric delivery of packs for balanced resuscitation are augmented with additional coagulation therapeutics given to treat established coagulopathies as diagnosed by

viscoelastic or conventional coagulation tests [27, 28, 52–56]. These therapies might include fibrinogen concentrates (or cryoprecipitate), platelet concentrates, procoagulant concentrates or tranexamic acid. This strategy, graphically illustrated in Figs. 1 and 2, allows continuous reassessment for the development of dilutional resuscitation-induced coagulopathy and treatment of any established coagulation disorders [57–59]. As above, it is important to contextualise the results of coagulation tests in the context of the known disease state (trauma, PPH, CLD), and to tailor treatments appropriately.

Prothrombin complex concentrates (PCCs) have been considered in some MHPs, though their role remains unclear. Four-factor (factor II, factor VII, factor IX, and factor X) PCC is mainly indicated for vitamin K antagonist reversal [60], but is sometime used off-label to provide vitamin-K-dependent coagulation factors in different clinical settings. Depending on the specific PCC, the products also contain small amounts of proteins C, S and Z, unfractionated heparin or antithrombin. Although several retrospective propensity-matched studies suggested that PCCs might improve survival and reduce total blood product consumption [61–64],



the PROCOAG trial [65] has recently shown clear unfavourable risk–benefit of empiric PCC administration in trauma patients. Indeed, in 327 trauma patients at risk of massive transfusion, the empiric administration of four-factor PCC—administered in combination with FFP—failed to reduce total blood product consumption, and significantly increased thromboembolic events compared to placebo (relative risk, 1.48 [95% CI 1.04–2.10]; $p=0.03$).

Similarly, although haemorrhage is exacerbated by acute fibrinogen deficiency, the CRYOSTAT-2 trial [66] has shown that an early and empirical high dose of cryoprecipitate (3 pools; 6-g fibrinogen equivalent) in addition to standard care within 3 h of injury did not improve all cause 28-day mortality (odds ratio (OR) 0.96 [95% confidence interval (CI) 0.75–1.23]; $p=0.74$).

Both trials highlight that empiric administration of coagulation factor concentrates is no longer recommended.

Patient management following bleeding and massive transfusion

After massive transfusion and haemorrhage control, patients are in a dramatically altered and complex physiologic state requiring close monitoring and expert care to reduce further complications and optimise outcomes. Widespread activation of the immune system may lead to a systemic inflammatory state, which can be dysregulated and followed by immune suppression and sepsis [67, 68]. In addition, a hyperdynamic state with high cardiac output and vasodilatation, which may mask ongoing hypovolaemia, may follow haemorrhagic shock. Myocardial ischaemia during profound haemorrhagic shock may cause cardiac dysfunction, which may be difficult to separate from other shocked states. Finally, the initial bleeding-associated coagulopathy may be followed by a rebound hypercoagulability with compensatory haemostatic activation and a prothrombotic state [14]. This transition can occur very early in the clinical course, and may be exacerbated by delayed or excessive administration of procoagulants or antifibrinolytics [69].

Circulatory support

Patients may continue to require volume resuscitation after massive transfusion because of capillary leakage related to vasodilation and increased endothelial permeability. Liberal use of crystalloids in traumatic haemorrhagic shock is associated with increased mortality and increased endothelial permeability, which may be related to increased shedding of the glycocalyx and breakdown of adherent and tight junctions [70]. Crystalloids should, therefore, be used judiciously. RBC transfusions may be appropriate if haemoglobin levels are low. The use of protein-rich fluids such as plasma compared to crystalloids has been associated with restoration in the thickness of the glycocalyx in experimental trauma models [71–73]. Studies in human trauma patients similarly suggest a beneficial role for plasma in supporting glycocalyx integrity, with indirect evidence of decreased glycocalyx shedding [74, 75].

Trauma or post-surgical patients who have suffered severe haemorrhagic shock develop hyperdynamic physiology with a distributive shock picture due to the systemic inflammatory response. Early vasopressor administration is often required to maintain perfusion pressures. This may mask relative or absolute hypovolaemia. In addition, secondary myocardial injury from ischaemia and inflammation can also occur after profound shock, as evidenced by elevated troponin levels within 24–48 h, leading to cardiac dysfunction [76, 77]. Early electrolyte abnormalities such as hyperkalaemia and hypocalcaemia may compound this. With an additional component of cardiogenic shock, inotropic agents (like milrinone, dobutamine or epinephrine) may augment the support for the distributive and/or hypovolaemic shock. Management of these patients is, thus, complex, requiring a fine balance of fluids, vasopressors and inotropic agents, and evidence is limited in this area.

Thromboprophylaxis

Patients who have been in shock and undergone massive transfusion experience a rebound hypercoagulable state post-trauma. Studies have demonstrated a shift to a hypercoagulable state within 48 h after trauma, and possibly within 3–6 h of injury [78]. Venous thromboembolism occurs in up to 20% of trauma patients and remains high even with pharmacological thromboprophylaxis [79]. In traumatic brain injury, one potential reason explaining why the risk of thromboembolic event is high after major bleeding is the avoidance or delay of using pharmacological thromboprophylaxis due to fear of worsening bleeding or re-bleeding complications, which further increases the risk of venous thromboembolism (VTE) [80, 81]. Indeed, whilst thromboprophylaxis has been shown to decrease the risk of VTE, there has been

some evidence that early initiation of thromboprophylaxis may be associated with the need for repeated surgical intervention [82]. In 2020, the Western Trauma Association released an algorithm for VTE prophylaxis after trauma to assist in determining which patients require pharmacologic prophylaxis, as well as the type and dosing [83]. Data regarding progression of intracranial haemorrhage after initiation of VTE prophylaxis are controversial. There is little evidence to suggest that standard doses of heparin or low-molecular-weight heparins are associated with post-traumatic bleeding outside of the central nervous system. Withholding VTE prophylaxis for an extended period out of concern for worsening bleeding has little evidence and may result in harm, as delays and missed doses of VTE prophylaxis are associated with increased morbidity [84]. There is strong evidence to support the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) [85]. Trauma patients may require intermediate or high doses of LMWH, as recent evidence suggests that LMWH resistance may be common in severely injured patients related to antithrombin deficiency [79]. This may be another factor contributing to the high incidence of VTE despite current ‘best practice’ in chemoprophylaxis. Unfortunately, there is currently little evidence to guide optimal thromboprophylaxis management in non-trauma patients.

Although the role of mechanical thromboprophylaxis is still debated, with available data providing conflicting results [86, 87], the European guidelines recommend the use of mechanical prophylaxis for patients with contraindications for pharmacologic anticoagulation (Grade 1B), and suggest the use of intermittent pneumatic compression over graduated compression stockings (Grade 2B) [88, 89]. The American guidelines do not support the use of combination therapy over either pharmacologic therapy or compression therapy alone [90].

Anaemia

Anaemia is common amongst critically ill patients during convalescence. Studies have shown anaemia affects 70–80% of post-ICU patients, with nearly half remaining anaemic 6 months later [91]. The anaemia of critical illness is multifactorial, though both a low erythropoietin (EPO) level, iatrogenic blood loss and a functional iron deficiency (orchestrated by high hepcidin levels) are key mediators [92]. For those patients that survive following massive transfusion, blood loss and even greater iron depletion add to the anaemia, which may limit a patient's ability to engage with rehabilitation and recovery. Proactive management of ICU-related anaemia through the use of EPO or iron has been suggested but remains uncertain and controversial [93]. The European

guidelines do not recommend the use of either EPO or iron in ICU patients [94], as EPO might increase the risk of thrombosis in patients with procoagulant states, and iron may be at least inefficient (or dangerous) in patients with systemic inflammation.

Additional considerations

1. *Individualising treatment algorithms*

It is important to note that protocols designed to treat patients with one source of massive haemorrhage, like trauma, for example, may not be readily adaptable to others. In addition, even in patients with the same underlying cause of haemorrhage, unique variation in the response to transfusion and treatment protocols may reflect additional factors at play in the pathophysiologic processes at play. Two recent articles [95, 96] highlight the existence of unique patient endotypes that may aid in identifying patients that will respond to various forms of resuscitation. These studies suggest that whilst MHPs may be validated on data from patients within those RCTs, there remains variability in patient responses that require consideration for individualising treatment algorithms. Best practise guidelines must, therefore, incorporate an understanding of the heterogeneity of patients and their treatment responses related to MHPs to truly improve outcomes.

2. *Resuscitative endovascular balloon occlusion of the aorta for exsanguinating haemorrhage (REBOA)*

As major haemorrhage is the most common cause of preventable death after trauma, Jansen et al. [97] have conducted a pragmatic Bayesian RCT to assess the effectiveness of REBOA on mortality. Ninety trauma patients with exsanguinating haemorrhage were randomised to receive either REBOA+standard of care or standard of care alone. The authors have shown that a strategy associating REBOA and standard care in the emergency department did not reduce mortality, and may even increase mortality compared with standard care alone (54% versus 42%; OR 1.58 [95% CI 0.72–3.52]; posterior probability of an OR > 1 [indicating increased odds of death with REBOA], 86.9%).

3. *The search for a “holy grail” anticoagulant*

The various causes of massive haemorrhage in critically ill patients are challenging to prevent, yet those cases associated with therapeutic anticoagulation represent one that may be mitigated through development of better medications. The search for a “holy grail” anticoagulant that is able to prevent thrombotic events without affecting overall haemostasis, and therefore without increased risk of bleeding risk,

is ongoing. To date, almost all conventional anticoagulants inhibit factors II or X; and, given the essential role of these factors in maintaining haemostasis under steady-state conditions, their use carries an increased risk of bleeding that is not insignificant. Recent studies have suggested that targeting other coagulation factors may avoid this risk. The contact phase (intrinsic) pathway is generally non-essential for maintaining physiologic haemostasis but takes part in the development of pathologic thrombosis. Thus, some have suggested that inhibitors targeting factors XI (FXI) or XII may display an antithrombotic effect without increasing the risk of bleeding [86–89]. New strategies have been developed to target FXI, including use of antisense oligonucleotides (ASO), which reduce FXI hepatic synthesis, or blocking FXI activation or activity with antibodies, aptamers or other small molecules [90]. FXI inhibition will likely require fine-tuning, as severe FXI deficiency might result in a higher risk of minor—mucosal (oropharynx/nasopharynx and genitourinary tract)—bleeding after trauma or surgery, given the fibrinolytic activity [90]. Nevertheless, the clinical utility of three classes of contact pathway inhibitors is currently being evaluated in phase 2 and 3 trials in various clinical situations (Table 2).

Conclusion

Bleeding remains a common complication encountered in critical care and necessitates an understanding of the pathophysiology of various coagulopathic conditions to provide appropriate patient care. The diagnosis and evaluation of bleeding and haemorrhagic shock may be difficult and relies on a combination of clinical and laboratory parameters. Patients with massive haemorrhage are best supported using major haemorrhage protocols developed by multidisciplinary teams to allow for a rapid and coordinated response. After massive transfusion, management is complex and requires an understanding of the multiple pathological processes involved. More research is required, especially in non-traumatic causes of haemorrhage. Nevertheless, large reductions in mortality, complications, resource utilisation and waste can be achieved with a planned, multidisciplinary, evidence-based approach to major haemorrhage [98].

Author details

¹ Department of Pathology and Laboratory Medicine, Center for Transfusion and Cellular Therapies, Emory University School of Medicine, Atlanta, GA, USA.

² Centre for Trauma Sciences, Queen Mary University of London, London, UK.

³ Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. ⁴ Nuffield Department of Clinical and Laboratory Sciences, Radcliffe Department of Medicine, Oxford University, Oxford, UK. ⁵ Department of Intensive Care and Laboratory of Translational Intensive

Care, Erasmus Medical Center, Rotterdam, The Netherlands. ⁶ Department of Anaesthesiology, Intensive Care and Pain Clinic, Vall d'Hebron Trauma, Rehabilitation and Burns Hospital, Autonomous University of Barcelona, Passeig de La Vall d'Hebron 119-129, 08035 Barcelona, Spain. ⁷ Trauma and Transfusion Medicine Research Center, University of Pittsburgh, Pittsburgh, PA, USA. ⁸ Department of Pathology, Duke University School of Medicine, Durham, NC, USA. ⁹ Amsterdam University Medical Centers, Amsterdam, The Netherlands. ¹⁰ Service de Médecine Intensive-Réanimation, Department of Intensive Care, Nouvel Hôpital Civil, Université de Strasbourg (UNISTRA), 1, Place de L'Hôpital, 67091 Strasbourg Cedex, France.

Funding
NA.

Declarations

Conflicts of interest

CLM has nothing to disclose. KB has received grants from Werfen GmbH Ltd. NC has received study grants from national agencies: DSTL, Wellcome Trust, MRC, and Investigator led grants from commercial companies: CSL Behring, SOBI. She has received honoraria for lectures from the Limbic and support for attending meetings from LFB, CSL Behring and SOBI. NC participates on an Advisory Board from Octapharma. NPJ has nothing to disclose. LMM has received honoraria for lectures from Octapharma, Ferrer Hospital (Haemonetics) and Werfen. She has received support for attending meetings and/or travel from ESAIC and Croatian Society of Anesthesiology. MDN has received grants from National Institutes of Health, National Institute of General Medical Services, Haemonetics, Alexion and Instrumentation Laboratories, honoraria for lectures from Haemonetics and Takeda, payment for expert testimony from Romanucci Blandon Law and Matis Baum O'Connor, support for attending meetings and/or travel from Takeda; participates on a Data Safety Monitoring Board or Advisory Board from NHLBI CONNECTS Steering Committee; is the Chief Medical Officer, Haima Therapeutics, and has Patents planned, issued or pending (US Patent 11,408,844; US Patent 9,072,760). BS has received book royalties from Elsevier, consulting fees from Chilled Platelets Study and supporting fees for attending meetings from Biomedical Excellence for Safer Transfusion. APJV has nothing to disclose. JH has received honoraria for lectures from Asahi Kasei, Diagnostica Stago, Pfizer PFE and Sanofi Aventis France.

Ethical disclosure

This study has been authorised by ethical committee (Comité de Protection des Personnes Nord Ouest IV 2018-A03446-49).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Received: 8 September 2023 Accepted: 5 December 2023
Published online: 08 January 2024

References

- Hooper N, Armstrong TJ (2023) Hemorrhagic. *ShockStatPearls*, Treasure Island
- Lauzier F, Arnold D, Rabbat C (2012) In medical-surgical ICU patients, major bleeding is common but independent of heparin prophylaxis. *Crit Care* 16(Suppl 1):P435
- Russell L, Holst LB, Kjeldsen L, Stensballe J, Perner A (2017) Risks of bleeding and thrombosis in intensive care unit patients with haematological malignancies. *Ann Intensive Care* 7:119
- Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 3:692–694
- Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, Schochl H, Hunt BJ, Sauaia A (2021) Trauma-induced coagulopathy. *Nat Rev Dis Primers* 7:30
- Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, Khan S, De'ath HD, Allard S, Hart DP, Pasi KJ, Hunt BJ, Stanworth S, MacCallum PK, Brohi K (2013) The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost* 11:307–314
- Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K (2012) Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 10:1342–1351
- de Lloyd L, Jenkins PV, Bell SF, Mutch NJ, Martins Pereira JF, Badenes PM, James D, Ridgeway A, Cohen L, Roberts T, Field V, Collis RE, Collins PW (2023) Acute obstetric coagulopathy during postpartum hemorrhage is caused by hyperfibrinolysis and dysfibrinogenemia: an observational cohort study. *J Thromb Haemost* 21:862–879
- Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, de Prost D, Group PPHS (2007) The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 5:266–273
- Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis (2010) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 8:202–204
- Ow TW, Fatourou E, Rabinowich L, van den Boom B, Nair S, Patel VC, Hogan B, McPhail M, Roberts LN, Bernal W (2022) Prevalence of bleeding and thrombosis in critically ill patients with chronic liver disease. *Thromb Haemost* 122:1006–1016
- van den Boom BP, Lisman T (2022) Pathophysiology and management of bleeding and thrombosis in patients with liver disease. *Int J Lab Hematol* 44(Suppl 1):79–88
- Roberts LN (2021) Rebalanced hemostasis in liver disease: a misunderstood coagulopathy. *Hematol Am Soc Hematol Educ Progr* 2021:485–491
- Helms J, Iba T, Connors JM, Gando S, Levi M, Mezzani F, Levy JH (2023) How to manage coagulopathies in critically ill patients. *Intensive Care Med* 49:273–290
- Levi M, Scully M (2018) How I treat disseminated intravascular coagulation. *Blood* 131:845–854
- Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ (2007) Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 3:138–153
- Hunt BJ (2014) Bleeding and coagulopathies in critical care. *N Engl J Med* 370:847–859
- Botrel T, Cunat S, Helms J, Lemarie J, Gaillon J, Preau S, Favory R, Thille AW, Boissier F, Maury E, Joffre J, Ait-Oufella H (2023) Extracranial anticoagulant related bleedings admitted to intensive care units: a French multicenter retrospective study. *Crit Care* 27:312
- Mutschler M, Nienaber U, Brockamp T, Wafaisade A, Fabian T, Paffrath T, Bouillon B, Maegele M, TraumaRegister DGU (2013) Renaissance of base deficit for the initial assessment of trauma patients: a base deficit-based classification for hypovolemic shock developed on data from 16,305 patients derived from the TraumaRegister DGU(R). *Crit Care* 17:R42
- Helms J, Curtiaud A, Severac F, Merdji H, Angles-Cano E (2023) Dynamic longitudinal increase in D-dimers: an early predictor of bleeding complications in ECMO. *Intensive Care Med* 49:1416
- Li C, Zhao Q, Yang K, Jiang L, Yu J (2019) Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. *J Thorac Dis* 11:1170–1181
- Amgalan A, Allen T, Othman M, Ahmadzia HK (2020) Systematic review of viscoelastic testing (TEG/ROTEM) in obstetrics and recommendations from the women's SSC of the ISTH. *J Thromb Haemost* 18:1813–1838
- Collins PW, Cannings-John R, Bruynseels D, Mallaiah S, Dick J, Elton C, Weeks AD, Sanders J, Aawar N, Townson J, Hood K, Hall JE, Collis RE (2017) Viscoelastic-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. *Br J Anaesth* 119:411–421

24. Al Moosawi M, Trudeau J, Smith T, Lefebvre A, Shih AW (2021) ROTEM in the setting of liver transplant surgery reduces frozen plasma transfusion. *Transfus Apher Sci* 60:103125
25. Zampieri RPC, Amorim TC, Queiroz VNF, Lira JDO, Costa LGV, Takaoka F, Juffermans NP, Neto AS (2018) Association between viscoelastic tests-guided therapy with synthetic factor concentrates and allogenic blood transfusion in liver transplantation: a before-after study. *BMC Anesthesiol* 18:198
26. Levrat A, Gros A, Rugeri L, Inaba K, Floccard B, Negrier C, David JS (2008) Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. *Br J Anaesth* 100:792–797
27. Rossaint R, Afshari A, Bouillon B, Cerny V, Cimpoesu D, Curry N, Duranteau J, Filipescu D, Grotte O, Gronlykke L, Harrois A, Hunt BJ, Kaserer A, Komadina R, Madsen MH, Maegele M, Mora L, Riddez L, Romero CS, Samama CM, Vincent JL, Wiberg S, Spahn DR (2023) The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. *Crit Care* 27:80
28. Kietai S, Ahmed A, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Godier A, Haas T, Jacob M, Lance MD, Llau JV, Meier J, Molnar Z, Mora L, Rahe-Meyer N, Samama CM, Scarlatescu E, Schlump C, Wikkelso AJ, Zacharowski K (2023) Management of severe peri-operative bleeding: guidelines from the European Society of Anaesthesiology and Intensive Care: second update 2022. *Eur J Anaesthesiol* 40:226–304
29. Erdoes G, Faraoni D, Koster A, Steiner ME, Ghadimi K, Levy JH (2023) Perioperative considerations in management of the severely bleeding coagulopathic patient. *Anesthesiology* 138:535–560
30. Muldowney M, Aichholz P, Nathwani R, Stansbury LG, Hess JR, Vavilala MS (2022) Advances in hemorrhage control resuscitation. *Curr Opin Anaesthesiol* 35:176–181
31. Vlaar APJ, Dionne JC, de Bruin S, Wijnberge M, Raasveld SJ, van Baarle F, Antonelli M, Aubron C, Duranteau J, Juffermans NP, Meier J, Murphy GJ, Abbasciano R, Muller MCA, Lance M, Nielsen ND, Schoch H, Hunt BJ, Cecconi M, Oczkowski S (2021) Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 47:1368–1392
32. Pham HP, Shaz BH (2013) Update on massive transfusion. *Br J Anaesth* 111(Suppl 1):i71–82
33. de Bruin S, Eggermont D, van Bruggen R, de Korte D, Scheeren TWL, Bakker J, Vlaar APJ (2022) Transfusion practice in the bleeding critically ill: an international online survey-The TRACE-2 survey. *Transfusion* 62:324–335
34. Wiersum-Osselton JC, Whitaker B, Grey S, Land K, Perez G, Rajbhandary S, Andrzejewski C Jr, Bolton-Maggs P, Lucero H, Renaudier P, Robillard P, Santos M, Schipperus M (2019) Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. *Lancet Haematol* 6:e350–e358
35. Bosboom JJ, Klanderman RB, Migdady Y, Bolhuis B, Veelo DP, Geerts BF, Murphy MF, Vlaar APJ (2019) Transfusion-associated circulatory overload: a clinical perspective. *Transfus Med Rev* 33:69–77
36. Ruseckaite R, McQuilten ZK, Oldroyd JC, Richter TH, Cameron PA, Isbister JP, Wood EM (2017) Descriptive characteristics and in-hospital mortality of critically bleeding patients requiring massive transfusion: results from the Australian and New Zealand Massive Transfusion Registry. *Vox Sang* 112:240–248
37. Karameh H, Bruoha S, Taha L, Tabi M, Farkash R, Karimi M, Hamayel K, Perel N, Steinmetz Y, Marmor D, Manassra M, Maller T, Hitter R, Amsalem I, Glikson M, Asher E (2023) Outcomes of patients treated with blood transfusion in a contemporary tertiary care medical center intensive cardiac care unit. *J Clin Med* 12:1304
38. Halmin M, Chiesa F, Vasan SK, Wikman A, Norda R, Rostgaard K, Vesterager Pedersen OB, Erikstrup C, Nielsen KR, Titlestad K, Ullum H, Hjalgrim H, Edgren G (2016) Epidemiology of massive transfusion: a binational study from Sweden and Denmark. *Crit Care Med* 44:468–477
39. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB (2007) The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 63:805–813
40. Halmin M, Bostrom F, Brattstrom O, Lundahl J, Wikman A, Ostlund A, Edgren G (2013) Effect of plasma-to-RBC ratios in trauma patients: a cohort study with time-dependent data*. *Crit Care Med* 41:1905–1914
41. Mesar T, Larentzakis A, Dzik W, Chang Y, Velmahos G, Yeh DD (2017) Association between ratio of fresh frozen plasma to red blood cells during massive transfusion and survival among patients without traumatic injury. *JAMA Surg* 152:574–580
42. Cardigan R, Latham T, Weaver A, Yazer M, Green L (2022) Estimating the risks of prehospital transfusion of D-positive whole blood to trauma patients who are bleeding in England. *Vox Sang* 117:701–707
43. Seheult JN, Stram MN, Pearce T, Bub CB, Emery SP, Kutner J, Watanabe-Okochi N, Sperry JL, Takanashi M, Triulzi DJ, Yazer MH (2021) The risk to future pregnancies of transfusing Rh(D)-negative females of childbearing potential with Rh(D)-positive red blood cells during trauma resuscitation is dependent on their age at transfusion. *Vox Sang* 116:831–840
44. Gammon RR, Meena-Leist C, Al Mozaian N, Cruz J, Hartwell E, Lu W, Karp JK, Noone S, Orabi M, Tayal A, Bocquet C, Tanhehco Y (2023) Whole blood in civilian transfusion practice: a review of the literature. *Transfusion* 63:1758–1766
45. Mack JP, Miles J, Stolla M (2020) Cold-stored platelets: review of studies in humans. *Transfus Med Rev* 34:221–226
46. Meneses E, Boneva D, McKenney M, Elkbuli A (2020) Massive transfusion protocol in adult trauma population. *Am J Emerg Med* 38:2661–2666
47. Sommer N, Schnuriger B, Candinas D, Haltmeier T (2019) Massive transfusion protocols in nontrauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg* 86:493–504
48. Hu P, Uhlich R, Black J, Jansen JO, Kerby J, Holcomb JB (2021) A new definition for massive transfusion in the modern era of whole blood resuscitation. *Transfusion* 61(Suppl 1):S252–S263
49. Foster JC, Sappenfield JW, Smith RS, Kiley SP (2017) Initiation and termination of massive transfusion protocols: current strategies and future prospects. *Anesth Analg* 125:2045–2055
50. Camazine MN, Hemmila MR, Leonard JC, Jacobs RA, Horst JA, Kozar RA, Bochicchio GV, Nathens AB, Cryer HM, Spinella PC (2015) Massive transfusion policies at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program. *J Trauma Acute Care Surg* 78:S48–53
51. Ngatuvi M, Zagales I, Sauder M, Andrade R, Santos RG, Bilski T, Kornblith L, Elkbuli A (2023) Outcomes of transfusion with whole blood, component therapy, or both in adult civilian trauma patients: a systematic review and meta-analysis. *J Surg Res* 287:193–201
52. Casu S (2021) Simplified treatment algorithm for the management of trauma-induced hemorrhage without viscoelastic testing. *Trauma Surg Acute Care Open* 6:e000779
53. Bugaev N, Como JJ, Golani G, Freeman JJ, Sawhney JS, Vatsaas CJ, Yorkgitis BK, Kreiner LA, Garcia NM, Aziz HA, Pappas PA, Mahoney EJ, Brown ZW, Kasotakis G (2020) Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg* 89:999–1017
54. Blaine KP, Steurer MP (2019) Viscoelastic monitoring to guide the correction of perioperative coagulopathy and massive transfusion in patients with life-threatening hemorrhage. *Anesthesiol Clin* 37:51–66
55. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, Brooks A, Rourke C, Gillespie S, Murphy J, Maroni R, Vulliamy P, Henriksen HH, Pedersen KH, Kolstadbraaten KM, Wirtz MR, Kleinvelde DJB, Schafer N, Chinna S, Davenport RA, Naess PA, Goslings JC, Eaglestone S, Stanworth S, Johansson PI, Gaarder C, Brohi K (2021) Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. *Intensive Care Med* 47:49–59
56. Baksaas-Aasen K, Van Dieren S, Balvers K, Juffermans NP, Naess PA, Rourke C, Eaglestone S, Ostrowski SR, Stensballe J, Stanworth S, Maegele M, Goslings JC, Johansson PI, Brohi K, Gaarder C, collaborators TI (2019) Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage: a prospective observational multicenter study. *Ann Surg* 270:1178–1185
57. Grolinger K, Pérez-Ferrer A, Dirkmann D, Saner F, Maegele M, Calatayud AAP, Kim TY (2019) The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol* 72:297–322
58. Hartmann J, Hermelin D, Levy JH (2023) Viscoelastic testing: an illustrated review of technology and clinical applications. *Res Pract Thromb Haemost* 7:100031

59. Zhu Z, Yu Y, Hong K, Luo M, Ke Y (2022) Utility of viscoelastic hemostatic assay to guide hemostatic resuscitation in trauma patients: a systematic review. *World J Emerg Surg* 17:48
60. Bouzat P, Hunt BJ, Juffermans NP (2023) Four-factor prothrombin complex concentrate in trauma patients. *Intensive Care Med* 49:1242–1244
61. Jehan F, Aziz H, O'Keeffe T, Khan M, Zakaria ER, Hamidi M, Zeeshan M, Kulvatunyou N, Joseph B (2018) The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: a propensity matched analysis. *J Trauma Acute Care Surg* 85:18–24
62. Zeeshan M, Hamidi M, Feinstein AJ, Gries L, Jehan F, Sakran J, Northcutt A, O'Keeffe T, Kulvatunyou N, Joseph B (2019) Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: a nationwide propensity-matched analysis. *J Trauma Acute Care Surg* 87:274–281
63. Joseph B, Aziz H, Pandit V, Hays D, Kulvatunyou N, Yousuf Z, Tang A, O'Keeffe T, Green D, Friese RS, Rhee P (2014) Prothrombin complex concentrate versus fresh-frozen plasma for reversal of coagulopathy of trauma: is there a difference? *World J Surg* 38:1875–1881
64. Joseph B, Khalil M, Harrison C, Swartz T, Kulvatunyou N, Haider AA, Jokar TO, Burk D, Mahmoud A, Latif R, Rhee P (2016) Assessing the efficacy of prothrombin complex concentrate in multiply injured patients with high-energy pelvic and extremity fractures. *J Orthop Trauma* 30:653–658
65. Bouzat P, Charbit J, Abback PS, Huet-Garrigue D, Delhay N, Leone M, Marcotte G, David JS, Levrat A, Asehnoune K, Pottecher J, Duranteau J, Courvalin E, Adolle A, Sourd D, Bosson JL, Riou B, Gauss T, Payen JF, Group PS (2023) Efficacy and safety of early administration of 4-factor prothrombin complex concentrate in patients with trauma at risk of massive transfusion: the PROCOAG Randomized Clinical Trial. *JAMA* 329:1367–1375
66. Davenport R, Curry N, Fox EE, Thomas H, Lucas J, Evans A, Shanmugaranjan S, Sharma R, Deary A, Edwards A, Green L, Wade CE, Bengier JR, Cotton BA, Stanworth SJ, Brohi K, Investigators C-P (2023) Early and empirical high-dose cryoprecipitate for hemorrhage after traumatic injury: the CRY-OSTAT-2 randomized clinical trial. *JAMA* 21 330(19):1882–1891. <https://doi.org/10.1001/jama.2023.21019>
67. Cabrera CP, Manson J, Shepherd JM, Torrance HD, Watson D, Longhi MP, Hoti M, Patel MB, O'Dwyer M, Nourshargh S, Pennington DJ, Barnes MR, Brohi K (2017) Signatures of inflammation and impending multiple organ dysfunction in the hyperacute phase of trauma: a prospective cohort study. *PLoS Med* 14:e1002352
68. Mira JC, Brakenridge SC, Moldawer LL, Moore FA (2017) Persistent inflammation, immunosuppression and catabolism syndrome. *Crit Care Clin* 33:245–258
69. Wirtz MR, Schalkers DV, Goslings JC, Juffermans NP (2020) The impact of blood product ratio and procoagulant therapy on the development of thromboembolic events in severely injured hemorrhaging trauma patients. *Transfusion* 60:1873–1882
70. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR (2011) A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. *Ann Surg* 254:194–200
71. Torres LN, Chung KK, Salgado CL, Dubick MA, Torres Filho IP (2017) Low-volume resuscitation with normal saline is associated with microvascular endothelial dysfunction after hemorrhage in rats, compared to colloids and balanced crystalloids. *Crit Care* 21:160
72. Torres LN, Sondeen JL, Ji L, Dubick MA, Torres Filho I (2013) Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats. *J Trauma Acute Care Surg* 75:759–766
73. Kozar RA, Peng Z, Zhang R, Holcomb JB, Pati S, Park P, Ko TC, Paredes A (2011) Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg* 112:1289–1295
74. Gruen DS, Brown JB, Guyette FX, Vodovotz Y, Johansson PI, Stensballe J, Barclay DA, Yin J, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Neal MD, Zuckerbraun BS, Billiar TR, Sperry JL, group PAs, (2020) Prehospital plasma is associated with distinct biomarker expression following injury. *JCI Insight* 5:e135350
75. Gruen DS, Guyette FX, Brown JB, Okonkwo DO, Puccio AM, Campwala IK, Tessmer MT, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Neal MD, Zuckerbraun BS, Yazer MH, Billiar TR, Sperry JL (2020) Association of prehospital plasma with survival in patients with traumatic brain injury: a secondary analysis of the PAMPer cluster randomized clinical trial. *JAMA Netw Open* 3:e2016869
76. Weber B, Lackner I, Gebhard F, Miclau T, Kalbitz M (2021) Trauma, a matter of the heart-molecular mechanism of post-traumatic cardiac dysfunction. *Int J Mol Sci* 22:737
77. De'Ath HD, Rourke C, Davenport R, Manson J, Renfrew I, Uppal R, Davies LC, Brohi K (2012) Clinical and biomarker profile of trauma-induced secondary cardiac injury. *Br J Surg* 99:789–797
78. Schellenberg M, Costantini T, Joseph B, Price MA, Bernard AC, Haut ER (2023) Timing of venous thromboembolism prophylaxis initiation after injury: Findings from the consensus conference to implement optimal VTE prophylaxis in trauma. *J Trauma Acute Care Surg* 94:484–489
79. Vincent LE, Talanker MM, Butler DD, Zhang X, Podbielski JM, Wang YW, Chen-Goodspeed A, Hernandez Gonzalez SL, Fox EE, Cotton BA, Wade CE, Cardenas JC (2022) Association of changes in antithrombin activity over time with responsiveness to enoxaparin prophylaxis and risk of trauma-related venous thromboembolism. *JAMA Surg* 157:713–721
80. Lu VM, Alvi MA, Rovin RA, Kasper EM (2020) Clinical outcomes following early versus late pharmacologic thromboprophylaxis in patients with traumatic intracranial hemorrhage: a systematic review and meta-analysis. *Neurosurg Rev* 43:861–872
81. Spano PJ 2nd, Shaikh S, Boneva D, Hai S, McKenney M, Elkbuli A (2020) Anticoagulant chemoprophylaxis in patients with traumatic brain injuries: a systematic review. *J Trauma Acute Care Surg* 88:454–460
82. Byrne JP, Witiw CD, Schuster JM, Pascual JL, Cannon JW, Martin ND, Reilly PM, Nathens AB, Seamon MJ (2022) Association of venous thromboembolism prophylaxis after neurosurgical intervention for traumatic brain injury with thromboembolic complications, repeated neurosurgery, and mortality. *JAMA Surg* 157:e215794
83. Ley EJ, Brown CVR, Moore EE, Sava JA, Peck K, Ciesla DJ, Sperry JL, Rizzo AG, Rosen NG, Brasel KJ, Kozar R, Inaba K, Martin MJ (2020) Updated guidelines to reduce venous thromboembolism in trauma patients: a Western Trauma Association critical decisions algorithm. *J Trauma Acute Care Surg* 89:971–981
84. Skarupa D, Hanna K, Zeeshan M, Madbak F, Hamidi M, Haddadin Z, Northcutt A, Gries L, Kulvatunyou N, Joseph B (2019) Is early chemical thromboprophylaxis in patients with solid organ injury a solid decision? *J Trauma Acute Care Surg* 87:1104–1112
85. Tran A, Fernando SM, Carrier M, Siegal DM, Inaba K, Vogt K, Engels PT, English SW, Kanji S, Kyeremanteng K, Lampron J, Kim D, Rochwerg B (2022) Efficacy and safety of low molecular weight heparin versus unfractionated heparin for prevention of venous thromboembolism in trauma patients: a systematic review and meta-analysis. *Ann Surg* 275:19–28
86. Fernando SM, Tran A, Cheng W, Sadeghirad B, Arabi YM, Cook DJ, Moller MH, Mehta S, Fowler RA, Burns KEA, Wells PS, Carrier M, Crowther MA, Scales DC, English SW, Kyeremanteng K, Kanji S, Kho ME, Rochwerg B (2022) VTE prophylaxis in critically ill adults: a systematic review and network meta-analysis. *Chest* 161:418–428
87. Helms J, Middeldorp S, Spyropoulos AC (2023) Thromboprophylaxis in critical care. *Intensive Care Med* 49:75–78
88. Duranteau J, Taccone FS, Verhamme P, Ageno W, Force EVGT (2018) European guidelines on perioperative venous thromboembolism prophylaxis: Intensive care. *Eur J Anaesthesiol* 35:142–146
89. Afshari A, Fenger-Eriksen C, Monreal M, Verhamme P, Force EVGT (2018) European guidelines on perioperative venous thromboembolism prophylaxis: Mechanical prophylaxis. *Eur J Anaesthesiol* 35:112–115
90. Schunemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaet R, Yepes-Nunez JJ, Zhang Y, Wiercioch W (2018) American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2:3198–3225
91. Bateman AP, McArdle F, Walsh TS (2009) Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. *Crit Care Med* 37:1906–1912
92. Hayden SJ, Albert TJ, Watkins TR, Swenson ER (2012) Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med* 185:1049–1057
93. Jelkmann I, Jelkmann W (2013) Impact of erythropoietin on intensive care unit patients. *Transfus Med Hemother* 40:310–318

-
94. Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, Aries P, Duranteau J, Juffermans NP, Meier J, Murphy GJ, Abbasciano R, Muller M, Shah A, Perner A, Rygaard S, Walsh TS, Guyatt G, Dionne JC, Cecconi M (2020) Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 46:673–696
95. Thau MR, Liu T, Sathe NA, O'Keefe GE, Robinson BRH, Bulger E, Wade CE, Fox EE, Holcomb JB, Liles WC, Stanaway IB, Mikacenic C, Wurfel MM, Bhatraju PK, Morrell ED (2023) Association of trauma molecular endotypes with differential response to transfusion resuscitation strategies. *JAMA Surg* 158:728–736
96. Wu J, Vodovotz Y, Abdelhamid S, Guyette FX, Yaffe MB, Gruen DS, Cyr A, Okonkwo DO, Kar UK, Krishnamoorthi N, Voinchet RG, Billiar IM, Yazer MH, Namas RA, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Zuckerbraun BS, Johansson PI, Stensballe J, Morrissey JH, Tracy RP, Wisniewski SR, Neal MD, Sperry JL, Billiar TR, Group PAs (2021) Multi-omic analysis in injured humans: patterns align with outcomes and treatment responses. *Cell Rep Med* 2:100478
97. Jansen JO, Hudson J, Cochran C, MacLennan G, Lendrum R, Sadek S, Gillies K, Cotton S, Kennedy C, Boyers D, Ferry G, Lawrie L, Nath M, Wilman S, Forrest M, Brohi K, Harris T, Lecky F, Moran C, Morrison JJ, Norrie J, Paterson A, Tai N, Welch N, Campbell MK, Group U-RS, Aylwin C, Bew D, Brooks A, Chinery J, Cowlam T, Frith D, George A, Hudson A, Johnstone P, Mahmood A, Novak A, O'Meara M, Reid S, Sattout A, Smith C, Stansfield T, Thompson J, (2023) Emergency department resuscitative endovascular balloon occlusion of the aorta in trauma patients with exsanguinating hemorrhage: the UK-REBOA randomized clinical trial. *JAMA*
98. Cole E, Weaver A, Gall L, West A, Nevin D, Tallach R, O'Neill B, Lahiri S, Allard S, Tai N, Davenport R, Green L, Brohi K (2021) A decade of damage control resuscitation: new transfusion practice, new survivors, new directions. *Ann Surg* 273(6):1215–1220. <https://doi.org/10.1097/SLA.0000000000003657>